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No. 06-1249

IN THE

Supreme Court of the United States

WYETH,

Petitioner,

–v.–

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO THE SUPREME COURT OF VERMONT

BRIEF OF DANIEL PAUL CARPENTER, AARON S. KESSELHEIM, JERRY AVORN, MARC T. LAW, AND DANIEL POLSKY AS *AMICI CURIAE* SUPPORTING RESPONDENT

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INTEREST OF AMICI CURIAE

Amici are professors who teach and write on the politics and economics of pharmaceutical regulation and physician-researchers who study prescription-medication use and policy.[1] *Amici* wish to ensure

[1] Pursuant to Supreme Court Rule 37.6, counsel for the *amici* certifies that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than the *amici* or their counsel has made a monetary

that the Court fully considers the social costs and benefits associated with the Vermont Supreme Court's holding in this case. *Amici* have no stake in the outcome of this case. They are filing this brief as individuals and not on behalf of the institutions with which they are affiliated.

Daniel Paul Carpenter is the Allie S. Freed Professor of Government, Faculty of Arts and Sciences, Harvard University. Before joining the faculty at Harvard, he taught political science at Princeton University and the University of Michigan. He is author of the book The Forging of Bureaucratic Autonomy: Networks, Reputations and Policy Innovation in Executive Agencies, 1862-1928 (Princeton University Press 2001), and a book manuscript, Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA (forthcoming, Cambridge University Press or Princeton University Press). He has written numerous technical and statistical articles on drug regulation, including Drug Review Deadlines and Subsequent Safety Problems, 358 New Eng. J. Med. 13:1354 (2008) (with Evan James Zucker and Jerry Avorn); Regulatory Errors with Endogenous Agendas, 51 Am. J. Pol. Sci. 4:835 (2007) (with Michael Ting); Protection Without Capture: Product Approval by a Politically Responsive, Learning Regulator, 98 Am. Pol. Sci. Rev. 4:613 (2004); Staff Resources Speed FDA Drug Review, 29 J. Health, Pol. Pol'y & L. 3 (2004); The Political Economy of FDA Drug Approval: Processing, Politics and Lessons for Policy, 23 Health Affairs 1:52 (2004); and Groups,

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contribution to the preparation or submission of this brief. Pursuant to Rule 37.3(a), letters of consent from both parties to the filing of this brief have been filed with the Clerk.

the Media, Agency Waiting Costs, and FDA Drug Approval, 46 Am. J. Pol. Sci. 3:490 (2002). Professor Carpenter has also written on the legislative history of the 1938 Food, Drug and Cosmetic Act in Policy Tragedy and the Emergence of Regulation: The Food, Drug and Cosmetic Act of 1938, 21 Stud. in Am. Pol. Dev. 2:149 (2007) (with Gisela Sin). He earned a Ph.D. in political science from the University of Chicago.

Aaron S. Kesselheim is an instructor in medicine at Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital, a major Harvard teaching institution. He graduated from Harvard College and received M.D. and J.D. degrees from the University of Pennsylvania School of Medicine and Law School and a Master's of Public Health degree from the Harvard School of Public Health. He is Board Certified in internal medicine and manages a primary-care clinic at Brigham and Women's Hospital, where he also attends on the general-medicine inpatient service. He has written many articles on drug regulation, including The Role of Litigation in Defining Drug Risks, 297 J. Am. Med. Ass'n 308 (2007) (with J. Avorn); Confidentiality Laws and Secrecy in Medical Research: Improving Access to Drug Safety Data, 26 Health Affairs 483 (2007) (with M. Mello); The Variability and Quality of Medication Container Labels, 167 Archives of Internal Med. 1760 (2007) (with W. Shrank et al.); and Pharmaceutical Promotion to Physicians and First Amendment Rights, 358 New Eng. J. Med. 1727 (2008) (with J. Avorn). His research focuses on the effects of intellectual property laws and government regulatory policies on pharmaceutical development, the drug-

approval process, and the costs and availability of therapeutic entities both domestically and in resource-poor settings. He has also investigated how other legal issues affect the American health care system, including expert testimony in malpractice cases, health care fraud, and insurance reimbursement practices. He is a member of the New York State Bar and is a patent attorney.

Jerry Avorn is a professor of medicine at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, geriatrician, and drug epidemiologist, he studies the intended and adverse effects of drugs, physician prescribing practices, and medication policy. He has served on several national and international panels as an expert on the determinants and consequences of medication use and is a past president of the International Society for Pharmacoepidemiology. Dr. Avorn has authored more than 200 papers in the medical literature on medication use and its outcomes and been named one of the most highly cited researchers in the area of medicine and the social sciences. His book, Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs, was published in 2004 by Knopf. He graduated from Columbia University, earned an M.D. from Harvard Medical School, and completed his training and certification in internal medicine within the Harvard teaching hospital system.

Marc T. Law is an assistant professor of economics in the Department of Economics at the University of Vermont. He has written several papers on the origins and evolution of food and drug regulation in the United States, including The

Origins of State Pure Food Regulation, 63 J. Econ. Hist. 1103 (2003); How Do Regulators Regulate? Enforcement of the Pure Food and Drugs Act, 1907-38, 22 J. L. Econ. & Org. 459 (2006); and The Determinants of Progressive Era Reform: The Pure Food and Drugs Act of 1906, in Corruption and Reform: Lessons from America's Economic History 319 (Edward Glaeser & Claudia Goldin eds., University of Chicago Press 2006) (with Gary D. Libecap). More generally, Dr. Law's research focuses on the role of asymmetric information about product quality in the rise of the U.S. regulatory state. He earned a Ph.D. in economics from Washington University, St. Louis.

Daniel Polsky is an associate professor of medicine in the Division of General Internal Medicine and an associate professor of health care systems in the Wharton School at the University of Pennsylvania and a senior fellow at the Leonard Davis Institute of Health Economics. In 2007-08, he was the senior economist on health issues at the President's Council of Economic Advisers. His research focuses on health insurance and economic evaluation of medical and behavioral health interventions. He is a coauthor of Economic Evaluation in Clinical Trials (Oxford University Press 2007). He received his Ph.D. in economics from the University of Pennsylvania in 1996.

SUMMARY OF ARGUMENT

Amici support the view of respondent and the Vermont Supreme Court that Congress has not chosen to preempt state-law failure-to-warn litigation. Economists writing in support of petitioner Wyeth (Petitioner's Economists) have asserted that the lack of preemption imposes heavy

social costs. Br. of J.E. Calfee et al. [hereinafter Economists' Br.]. That assertion is wrong. Empirical data and correct analysis demonstrate instead that Congress's refusal to foreclose state litigation has important social benefits.

State-law failure-to-warn litigation plays an essential role in promoting drug safety. Significant imbalances of safety-related information are inherent in the approval of pharmaceutical products. State-law failure-to-warn litigation mitigates that information asymmetry because it aligns the incentives of drug manufacturers and consumers by: (1) supplementing the FDA's inadequate resources and incentives to monitor comprehensively the performance of every drug on the market, (2) providing a strong incentive to drug manufacturers to change labeling unilaterally to respond to signals of health risks associated with their products, and (3) providing consumers with recourse in the event that drug manufacturers do not strengthen warnings about their products when appropriate.

State-law failure-to-warn litigation does not, as erroneously contended by Petitioner's Economists, exacerbate a perceived problem with the FDA's being overly cautious in drug approvals and labeling. In fact, such litigation provides incentives for the FDA to approve more drugs than it otherwise would and approve them more expeditiously.

Petitioner's Economists badly misconstrue the FDA's capabilities and incentives, and they ignore the notion that incentives for drug manufacturers to maximize profits may be misaligned with the ideal outcomes for public health. Petitioner's Economists incorrectly assume that the FDA is privy to perfect information, capable of enforcing its agenda with

the same level of authority before and after a drug is approved for the market, and monolithically incentivized to protect its reputation above all else by exercising undue caution. All three of those assumptions are incorrect. Information asymmetries, budget inadequacies, and regulatory realities limit the FDA's ability to enforce a concerted agenda, if it had one. Moreover, there are significant pressures on the FDA—from drug companies, patient advocates, members of Congress, the media, even investors in pharmaceutical companies—to approve drugs quickly, even if those drugs also may have potentially dangerous side effects. Further, even if the premise that FDA drug-approval policy is too risk-averse were not faulty, nothing supports Petitioner's Economists' treatment of the FDA's *labeling* policy as indistinguishable from its allegedly overcautious approval policy.

Nor is it correct to assume that the FDA can continuously optimize its regulatory standard throughout a drug's lifecycle. In reality, the FDA's tools for gathering post-approval information are relatively crude and ineffective, meaning the quality of information that the FDA receives for drugs once they reach the market may be severely limited. Crucial information about a drug's safety may become available only as a direct result of failure-to-warn litigation. And, after a drug is approved, FDA authority to compel labeling changes or further studies is substantially reduced. The lack of high-quality information and the limits on FDA enforcement power severely undermine the FDA's ability to act as an effective regulator of what physicians and patients know about a drug once it is on the market. Accordingly, the tort system encourages manufacturers to act reasonably in

warning physicians and patients about newly emerging risks and helps ensure that important risk information is provided to physicians, patients, and the FDA.

ARGUMENT

I. STATE FAILURE-TO-WARN LITIGATION PLAYS A CRITICAL ROLE IN PROMOTING DRUG SAFETY.

State failure-to-warn lawsuits are critical to promoting drug safety, particularly with respect to the level of precaution undertaken by drug manufacturers in how they present information about adverse events to physicians and patients. The contributions of tort law to product safety were recognized early on by leading thinkers of the law and economics movement, especially those associated with the Chicago School of economics.[2] The safety and efficiency benefits of state-law failure-to-warn suits are precipitated by a nuanced array of economic

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[2] See Landes et al., A Positive Economic Analysis of Products Liability, 14 J. Legal Stud. 535, 566 (1985) (concluding that "the economic structure of the common law of products liability . . . is in the main economically rational, much as [their] other studies have found with regard to other, and somewhat less controversial, areas of tort law and of the common law more broadly"); Landes et al., Tort Law as a Regulatory Regime for Catastrophic Personal Injuries, 13 J. Legal Stud. 417, 434 (1984) ("In view of the many criticisms that have been leveled against regulation, it would be a shame to give up on tort law as a method of regulating safety in cases of catastrophic accident without careful consideration of its actual and potential resources as a system of safety regulation."); Shavell, A Model of the Optimal Use of Liability and Safety Regulation, 15 RAND J. Econ. 271, 271 (1984) ("[N]either liability nor regulation is necessarily better than the other, and as is stressed, their joint use is generally socially advantageous.").

and structural forces, but all those forces are tied together by two fundamental concepts: incentives and information. The recourse provided by state failure-to-warn suits helps align producer incentives with consumer safety concerns and ensure that consumers have optimal information so that market transactions are more apt to be based on mutually beneficial exchanges between consumers and producers.

A. Failure-to-Warn Litigation Serves a Supplementary Administrative Function to Improve Oversight of Drug Safety Because Pharmaceutical Manufacturers Are in the Optimal Position to Identify Emerging Safety Concerns.

When a drug is approved by the FDA, it is approved based on a small number of studies in a modest number of subjects, some of whom may be disease-free volunteers and many of whom are far healthier than the patients for whom doctors usually write prescriptions. These studies may last only a brief time, sometimes as short as eight to sixteen weeks, even for drugs designed to be taken for a lifetime. This is possible because the effect that forms the basis for approval may be improvement of a laboratory test (*i.e.*, a surrogate marker) rather than real clinical outcomes. But requiring a drug to be studied in many thousands of patients over many years before approval could delay important new products from entering the market. Should FDA Drug and Medical Device Regulation Bar State Liability Claims? Hearing Before the H. Comm. on Oversight and Government Reform, 110th Cong. (2008) (statement of Aaron S. Kesselheim, Div.

of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hosp., Harvard Med. Sch.).

As a result, when the FDA approves a drug, it cannot fully certify its ongoing safety. *E.g.*, A Guide to Drug Safety Terms at FDA, April 11, 2008, http://www.fda.gov/consumer/updates/drugterms041108.html ("[E]ven with a rigorous evaluation process, some safety problems surface only after a drug has been on the market and has been used in a broader population."). Indeed, studies show that half of all drug withdrawals occur within two years after the drug was first approved. Lasser et al., Timing of New Black Box Warnings and Withdrawals for Prescription Medications, 287 J. Am. Med. Ass'n 2215, 2215 (2002). The FDA has two significant limitations that impede its ability to assure drug safety after a product is approved. First, as noted above, during the approval process, the manufacturer's clinical tests necessarily involve only a limited sample of patients and are often statistically powered to detect changes in clinical endpoints, rather than important adverse events that might arise. Thus, the FDA may not have a complete picture of the safety of drugs being considered for approval—and some rare side effects may escape detection altogether. See Kessler et al., A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims, 96 Geo. L.J. __, __ (2008) (forthcoming) [hereinafter Kessler, A Critical Examination] ("[P]re-approval testing generally is incapable of detecting adverse effects that occur infrequently, have long latency periods, or affect subpopulations not included or adequately represented in the studies (*e.g.*, the elderly, ethnic minorities and pregnant women)."). Second, as has been widely recognized for decades, the post-

marketing safety functions of the FDA have been severely underfunded, sharply reducing the effectiveness of such activities. The FDA thus, after approval, lacks the resources and capability to actively monitor evolving knowledge about a drug. *Id.*, at ____; J. Avorn, Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs 36 (2004) [hereinafter Avorn, Powerful Medicines].

The FDA often cannot uncover the latent risks of approved drugs, or would have to incur significant expenses—for which it does not have the budget—to do so.[3] Those discovery costs effectively limit the extent to which the FDA can ensure that the drug labels it approves when the drug is first marketed continue to warn consumers effectively about the potential consequences of a given treatment. Avorn, Powerful Medicines 169.[4]

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[3] An example of this issue surfaced in litigation relating to Zyprexa, a drug manufactured by Eli Lilly to treat schizophrenia and bipolar disorder that has also been linked to serious side effects like severe weight gain, increases in cholesterol and blood sugar, and diabetes. Berenson, Lilly Settles With 18,000 Over Zyprexa, N.Y. Times, Jan. 5, 2007, at C1 (discussing documents showing that "Lilly played down the risks of Zyprexa to doctors as the drug's sales soared after its introduction in 1996").

[4] See also Kessler et al., *supra*, at 8 ("The FDA's statutory and regulatory tools for gathering post-approval information are relatively crude and often ineffective, especially when contrasted with its tools for information gathering prior to approval. For that reason, the tort system has historically provided important information about these newly-emerging risks to physicians, patients and the FDA."). The 2007 FDA Amendments Act gave the FDA somewhat heightened authority to require postmarketing studies, Pub. L. No. 110-85, §901 et seq., 121 Stat. 823 (2007), but the FDA still has to know enough about the potential risk associated with a given drug to ask for

Pharmaceutical manufacturers, however, closely monitor the use of their products after FDA approval, organize postmarketing studies, and analyze voluntary spontaneous reports from physicians and other sources about adverse events arising in the course of therapy. Pharmaceutical manufacturers' sales representatives maintain frequent contact with physicians and hospitals to promote use of their products. The manufacturer is thus in the best position to learn about emerging safety concerns. By law, drug manufacturers are required to submit periodic reports of adverse events in certain categories relating to their products, 21 CFR §§310.305, 314.80 (2007), but the way pharmaceutical companies choose to define or fill out those categories may omit or underrepresent clinically significant safety problems.

Manufacturers often have considerable latitude regarding whether to study or not study a given adverse effect in the post-marketing setting, and even in the measurement and analysis of the safety data available to them. When safety issues emerge that suggest limiting the scope of use, or removing a drug from the market altogether, some pharmaceutical companies have chosen to downplay reports of side effects and obfuscate their periodic reports to the FDA. Psaty et al., Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment, 299 J. Am. Med. Ass'n 1813, 1814-1815 (2008); Psaty et al., Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis, 292 J. Am. Med. Ass'n

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these studies. It is too soon to determine how effective these measures will be.

2622, 2626-30 (2004). That conduct occurs because providing new safety information quickly and accurately to the FDA may cause the agency to recommend adding new warnings to the official label, or to remove the drug from the market altogether. Thus, use of the product might be reduced (or eliminated), and the manufacturer's profits will fall. Manufacturers have a duty to their shareholders to maximize profits.

State failure-to-warn litigation provides substantial penalties for manufacturers' decisions to hide or downplay reports of safety issues that emerge after a product reaches the market. Potential damage awards provide drug manufacturers with a strong incentive to expeditiously provide full and clear information to physicians and the FDA that otherwise may not come to light. Without such litigation, drug manufacturers would have a stronger incentive to act in their immediate financial interest and be less forthcoming in providing emerging safety-related data.

State tort lawsuits thus provide an incentive for drug manufacturers to fully disclose their knowledge of product risks to the FDA, improving its ability to strike the correct balance between Type I errors (failing to require a warning when that warning is necessary) and Type II errors (requiring a warning when that warning is not necessary). Further, state failure-to-warn suits encourage drug manufacturers to work with the FDA to ensure that labels accurately reflect the risks associated with a given treatment. Given the potential ambiguity and biased judgment calls inherent in drug risk assessment, the well-documented problems with companies' reporting of adverse events to the FDA, and the agency's

limited capacity to analyze the safety data it receives, state failure-to-warn suits are necessary to supplement the FDA's regulatory mission. As full information is critical to enabling physicians and patients to make the best possible decisions about medication use, such suits play a vital role in optimizing social welfare.

B. Failure-to-Warn Litigation Provides an Additional Deterrent Function Helping Promote Drug Safety by Encouraging Drug Manufacturers to Change Labeling Unilaterally to Respond to Risks.

State tort suits provide an additional incentive that complements the FDA—a deterrent mechanism that federal agencies like the FDA cannot replicate. The availability of state failure-to-warn litigation helps protect consumers when harmful consequences become apparent regarding drugs that have already been approved by the FDA. When such information becomes apparent to manufacturers and not the FDA, as is usual, manufacturers may not act appropriately with that information.

In the past, manufacturers have continued to promote their products to physicians and have engaged in strategies to downplay emerging safety concerns. See Berenson, For Merck, the Vioxx Paper Trail Won't Go Away, N.Y. Times, Aug. 21, 2005, at 3 ("Merck sales representatives [were] trained to view doctors' concerns about Vioxx's heart risks as 'obstacles' to be avoided or dismissed. Another marketing document taught representatives to play 'Dodgeball' when doctors voiced concerns."). Those efforts have been intended to induce consumers to continue using drugs that the manufacturer knows

have emerging underreported or unreported risks. Without failure-to-warn litigation, consumers would have no recourse in the event that aggressive marketing induced them or their prescribing physicians into sub-optimal behavior because the FDA has no mechanism for awarding damages. Physicians cannot act as learned intermediaries in assessing the risk-benefit profile of a drug if they do not have adequate risk information.

State tort lawsuits create the potential for losses (in the form of damages payments) in the face of corporate malfeasance. If the FDA were the only force regulating the drug market, drug manufacturers would have an incentive to exploit their information advantage to continue to promote drugs with important safety problems without proper warning. Given the immense power of the profit motive, a drug manufacturer could have strong incentives to sell a drug it knows to have underreported harmful consequences to recoup its investment and meet the demands of stockholders. Even under the current system, there is evidence that some drug manufacturers have attempted to hide information from the FDA to get approval to market their drugs. See, *e.g.*, *In re Baycol Prods. Litig.*, 218 F.R.D. 197 (D. Minn. 2003); *In re W. Va. Rezulin Litig.*, 585 S.E.2d 52, 58-59 (W. Va. 2003). Reducing the cost of concealing information (which would occur if state tort liability were removed) would encourage drug manufacturers to withhold critical safety information more often. Failure-to-warn litigation thus encourages manufacturers to advertise their products accurately and fairly.

The net effect of this complementary arrangement is the promotion of full and accurate

knowledge about drug risks and the minimization of misstatements or error in drug labeling. A significant literature chronicles the social welfare benefits of dual regulation of risky technologies.[5] For example, Professor William Buzbee of Emory University explains that "[t]he common law system's independence and private incentives to challenge the status quo are particularly valuable antidotes to complacency and ineffective regulation." Buzbee, Asymmetrical Regulation: Risk, Preemption, and the Floor/Ceiling Distinction, 82 N.Y.U. L. Rev. 1547, 1556 (2007). Accordingly, state-law failure-to-warn litigation serves as a valuable complement to FDA regulation.

C. By Harnessing the Forces of Decentralization, Failure-to-Warn Litigation Expedites the Diffusion of New and Potentially Vital Information on the Characteristics of New Drugs.

State tort-liability suits serve an essential role in facilitating the rapid transmission of information about drugs' properties. Given the decentralized nature of the court system, civil tort trials can help reveal the unexpected effects of drugs after they have been approved by the FDA by providing individuals with local recourse. As the FDA has limited scope and ability to evaluate drugs after they have gained approval, state tort liability suits play an extremely important role in ensuring that drugs on the market

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[5] See generally Landau, Redundancy, Rationality, and the Problem of Duplication and Overlap, 29 Pub. Rev. 346 (1969); J. Bendor, Parallel Systems: Redundancy in Government (1985); C.F.L. Heimann, Acceptable Risks: Politics, Policy, and Risky Technologies (1997); Ting, A Strategic Theory of Bureaucratic Redundancy, 47 Am. J. Pol. Sci. 274-292 (2003).

are safe and properly labeled. Litigation brought by individual patients can help uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in regulatory systems. Kesselheim and Avorn, The Role of Litigation in Defining Drug Risks, 297 J. Am. Med. Ass'n 308 (2007).

Furthermore, by forcing labeling issues under the microscope of the adversarial system, courts subject drugs to a powerful form of information gathering apart from the regulatory process. Indeed, the immense value of the adversarial system in gathering information that even a centralized body of experts might miss is a philosophical pillar of the U.S. court system. See, *e.g.*, Bernstein, Expert Witnesses, Adversarial Bias, and the (Partial) Failure of the Daubert Revolution, 93 Iowa L. Rev. 451, 457, n.28 (2008). Finally, the court system harnesses the power of market forces to catalyze the dissemination of information. Plaintiffs' failure-to-warn suits give lawyers an economic incentive to gather information that national regulatory bodies lack.

Conversely, the nontrivial costs of bringing a failure-to-warn suit acts as an additional filter on the legitimacy of the cases brought before the court as plaintiffs' attorneys will not recoup their investment if they undertake cases without a reasonable hope of success. FDA decisions and pronouncements can also play a significant role in juries' evaluation of failure-to-warn cases. Kessler, A Critical Examination, at __ (noting that a "drug company would have a powerful defense" when it is "able to argue to the jury that it complied with applicable FDA requirements and that the plaintiff is complaining about the absence of a

warning the FDA had rejected").[6] As unencumbered dissemination of information is key to effective safety regulation, state tort liability suits serve a vital economic function. Thus, while the FDA serves as the initial regulator of drug labeling, the state tort system plays a crucial role in assessing the FDA's errors and oversights.

II. PETITIONER'S ECONOMISTS FAIL TO DEMONSTRATE THAT PREEMPTION WOULD BE PREFERABLE TO PERMITTING STATE FAILURE-TO-WARN LITIGATION.

Petitioner's Economists attempt to show that Congress's decision not to preempt state failure-to-warn claims decreases social welfare by exacerbating error in the drug-labeling process. Their argument boils down to a three-step theory: (1) the FDA is overly cautious in drug *approval* because of political—specifically, reputational—pressures, (2) the FDA faces the same pressures and exercises the same excess caution in drug *labeling*, and (3) additional deterrence from state tort litigation exacerbates the detrimental effects from that excess caution. All of those steps are rebutted by empirical evidence and analysis.

A. A Framework for Evaluating the Types of Error and Social Costs at Issue

The costs at issue are those associated with two types of error. A Type I error would involve

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[6] As discussed further below, Petitioner's Economists completely ignore the potential symbiotic relationship between FDA regulation and litigation that has been documented in the relevant economic literature and write as though each process is performed without reference to the other.

approving a drug that should not have been approved or failing to require labeling verbiage when that verbiage is necessary; the associated cost is the decline in a patient's well-being from taking a drug that should not have been approved or taking an approved drug in the absence of critical warnings or contraindications.[7] A Type II error would involve failure to approve a beneficial drug or imposing verbiage that is not necessary; the associated cost is the decline in a patient's well-being resulting from *not* taking the drug because it was not approved or because of superfluous information ("overwarning"). The socially optimal approval or labeling standard is one that perfectly balances the expected cost of Type I errors and Type II errors.

To visualize the FDA's labeling calculus, think of the FDA assigning a probability that a given drug d (for example, Vioxx) causes a certain symptom s (for example, myocardial infarction) as P_{ds}. Let $Þ_s$ be the percentage of the general population that suffers from symptom s. Let P_{FDA} ($P_{FDA} > Þ_s$) be the "critical value" such that, when any drug-symptom pair is assigned a probability above P_{FDA}, the FDA requires the drug manufacturer to include verbiage relating to that drug-symptom pair (for example, "Vioxx may lead to myocardial infarction") on the drug's label.

Let P^* be the socially optimal labeling standard. In the absence of any biased political influence, P_{FDA} would be chosen so as to optimally balance the expected costs of Type I and Type II errors—that is, $P_{FDA} = P^*$.

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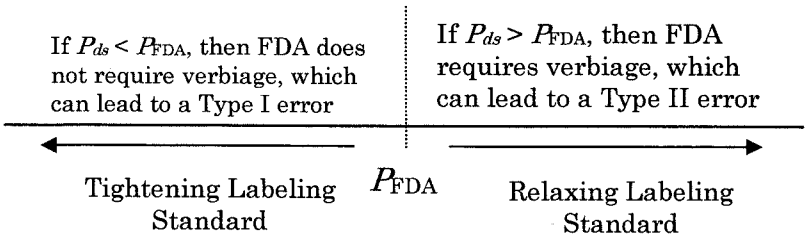
[7] A contraindication is a factor that makes use of a drug or medical procedure inadvisable.

When the FDA requires the drug manufacturer to include verbiage relating to a drug-symptom pair on the label, it exposes the patient to the possibility of a Type II error. Similarly, when the FDA does *not* require the drug manufacturer to include verbiage relating to a drug-symptom pair on the label, it exposes the patient to the possibility of a Type I error. As illustrated in Figure 1, as the FDA makes its labeling standard more stringent (that is, as P_{FDA} is moved to the left in the diagram), the probability of a Type I error is lessened and the probability of a Type II error is increased.

FIGURE 1: ERRORS AND COSTS ASSOCIATED WITH THE FDA'S LABELING STANDARD



A similar diagram could depict the issues facing the FDA in drug-approval decisions. Petitioner's Economists begin with the (untenable) premise that, in its drug-approval decisions, the FDA, due to political pressure, picks some critical value of P_{FDA} such that the balancing of error costs is suboptimal. In particular, they assert that the FDA tolerates too many Type II errors, causing $P_{FDA} < P^*$. They then leap to the assumption that the same situation prevails with regard to the FDA's drug-labeling decisions. Because there is no empirical or analytical support for those premises, nothing supports Petitioner's Economists' ultimate conclusions that

jury decisions in state failure-to-warn litigation exacerbates the problems caused by an overly cautious approach at the FDA and that preemption would thus provide an important safeguard against Type II errors.

B. There Is No Reason to Believe the FDA Is Overly Cautious in Labeling Standards.

Petitioner's Economists inaccurately ascribe motives to the FDA, making their conclusion that the FDA is unduly cautious when it comes to warning about drug safety concerns erroneous. In fact, the limited efficacy of the FDA as a regulatory body *after* a drug has been released to the market renders the FDA's incentives of ancillary importance.

1. There Is No Proof That the FDA Is Overly Cautious in Its Labeling Policy.

Petitioner's Economists repeatedly conflate the FDA's alleged *drug-approval* problem with its alleged *drug-labeling* problem, essentially treating the two issues as identical. As discussed further below, nothing supports the idea that today's FDA is overly cautious in drug approval. More germane to this case, Petitioner's Economists provide no empirical support for the proposition that the FDA is overly cautious with respect to its labeling policy.

Petitioner's Economists fail to provide any empirical evidence that the FDA is overly cautious with respect to its labeling policy and the FDA's excessive caution there leads to an inefficient level of Type II errors. The single relevant law review article cited, co-authored by one of Petitioner's Economists and a senior-assistant counsel for litigation at

Bristol-Myers Squibb, reads more like an advocacy piece. Its policy prescription—preemption of state tort liability with certain exceptions—is largely based on two anecdotal examples (DPT and Bendectin) that purport to show that "tort liability can create perverse incentives that actually harm social welfare." Viscusi et al., Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense, 24 Seton Hall L. Rev. 1437, 1480 (1994). Bendectin, however, was removed from the market 25 years ago, and the DPT anecdote has nothing to do with product-labeling issues. *Id.*, at 1470 (identifying DPT litigation as raising "design defect challenges"). To support their claim that the FDA is overly cautious regarding product labeling, Petitioner's Economists cite only a footnote in the law review article, which merely restates the central claim in their amicus brief that the FDA is overly cautious in its labeling calculus (again without any empirical support). See *id.*, at 1469 n.118. Finally, even the law review article does not advocate *blanket* preemption of state tort liability relating to drug labeling—the position now advocated by Petitioner's Economists. Instead, the article advocates several important exceptions to preemption, including fraud on the FDA and uses of drugs in ways not approved by the FDA (*i.e.*, "off-label" uses), *id.*, at 1478, which can account for over 70% of the prescriptions in some drug classes.[8]

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[8] Off-label use is central to a case brought by ten state attorneys general against Eli Lilly involving the drug Zyprexa. The lawsuit accuses Lilly of "running an illegal marketing campaign to promote Zyprexa for unapproved off-label uses, including treating children," and alleges that Lilly's campaign concealed risks, including diabetes, weight gain, and

The only other piece of evidence presented by Petioner's Economists is a May 2008 newspaper article relating to a single anecdote, Label on Merck Vaccine to Disclose a Death, Wall St. J., May 2, 2008, at B8, that purports to show that the FDA required Merck to include superfluous information on a label for Rotateq (a vaccine). The FDA required Merck to report on its label the death of a recipient of the drug due to an intestinal obstruction. *Ibid.* A Merck spokesperson claimed that the "rate of reported cases of intestinal obstruction, or intussusception, hasn't been greater than expected by chance alone." *Ibid.* But that claim, even if true, does not constitute proof that the FDA systematically imposes a suboptimal labeling standard. Using the framework depicted in Figure 1, Merck is merely claiming that the critical value used by the FDA, $P_{FDA,}$ is not significantly greater than the percentage of the population with intussusceptions, P_s. If the cost of a Type II error with respect to labeling policy is small relative to the cost of a Type I error, then the FDA's requirement that Merck include such verbiage may be consistent with the socially optimal (and very stringent) drug-labeling standard. Rotavirus vaccines have, in fact, been linked to intussusception in children, see, *e.g.*, Suspension of Rotavirus Vaccine After Reports of Intussusception—United States, 1999, 53(34) MMWR Weekly 786, Sept. 3, 2004, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5334a3.htm, making the warning a clinically relevant issue.

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cardiovascular problems. See Tenth State Sues Over Eli Lilly Drug, Wall St. J., Mar. 12, 2008, at B4.

2. Petitioner's Economists Overstate the FDA's Incentives for Caution and Ignore Evidence of Pressure for Faster Drug Approval and FDA Risk-Taking.

Petitioner's Economists' conclusions about FDA drug-labeling policy proceed from assertions about its drug-approval policy that are simply not true. They claim that, due to political pressure, the FDA's risk aversion leads it to withhold beneficial therapies from the American health system. That assertion relies on studies twenty years old or older, written in the 1970s, when European regulatory agencies approved some drugs (for example, beta-blockers) years before the FDA did. Numerous later studies show that the FDA no longer lags other countries in approving new drugs.[9] Indeed, in recent decades, the U.S. is frequently the first country to approve a new drug. Since the Prescription Drug User Fee Act (PDUFA), 21 U.S.C. §301 et seq., was enacted in 1992, the FDA has been required to adhere to strict deadlines for drug approval and has markedly

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[9] *E.g.*, Kessler et al., Approval of New Drugs in the United States. Comparison with the United Kingdom, Germany, and Japan, 276 J. Am. Med. Ass'n 22:1826, 1826 (1996) ("The analysis reveals that the United States and the United Kingdom have similar patterns of drug availability, although the United States has a number of therapies with significant public health benefits that are not yet available in the United Kingdom. The findings also show that the United States outpaces both Germany and Japan in approving important new drugs."); see also Rawson, Time Required for Approval of New Drugs in Canada, Australia, Sweden, the United Kingdom, and the United States in 1996-1998, 162 Can. Med. Ass'n J. 4:501, 503-504 (U.S. approval times shorter than Sweden, Canada, and Australia).

accelerated its speed of decision-making. By contrast, there is little evidence of scientifically inappropriate delayed decisions (or outright rejections) of important new products that have kept useful therapies from the American public.

Regulatory agencies like the FDA do take their reputation into account, but reputation cuts both ways. There is substantial political criticism when the FDA delays or blocks introduction of a new drug. For example, when the first therapies for AIDS were developed, political activists, along with congressional committees and politicians from both major parties, pressured the agency to accelerate its drug-approval process. From 1986 to 1998, FDA drug-approval times fell from an average of 24-30 months to 12 months. P. Hilts, Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation 278-279, (2003); Carpenter et al., Approval Times for New Drugs: Does the Source of Funding for FDA Staff Matter?, Health Affairs, Web Exclusive, W3-618-624, (2003) available at http://content.healthaffairs.org/cgi/reprint/hlthaff.w3.618v1 [hereinafter Carpenter et al., Web Exclusive]. In recent years, many politicians and activists have followed the AIDS-policy example and pressured the agency for quicker approvals and less stringent regulation of new therapies. Many newspaper editorial boards, including the Wall Street Journal, have joined this chorus. *E.g.*, Review & Outlook—Breast Cancer Reprieve, Wall St. J., Feb. 27, 2008, at A16; Review & Outlook—A Moral Test for the FDA, Wall St. J., Feb. 21, 2008, at A16.

Numerous empirical studies also show evidence of those patterns. They demonstrate a robust association between the strength of patient advocacy

groups and the speed of FDA drug approval. Controlling for the severity of the disease targeted by the drug, the greater the political organization of the patient advocates for the targeted disease, the faster the drug in question will be approved. Carpenter, The Political Economy of FDA Drug Approval: Processing, Politics, and Lessons for Policy, 23 Health Affairs 52, 56-60 (2004); see generally Carpenter, Groups, the Media, Agency Waiting Costs, and FDA Drug Approval, 46 Am. J. Pol. Sci. 3:490 (2002). Accordingly, in ignoring the potential for patient advocacy groups and other organized interests to lobby the FDA for faster drug approvals, Petitioner's Economists seriously overstate the FDA's incentive to be excessively cautious in drug-approval decisions.

The last two decades have also witnessed major policy changes—supported by the FDA and politicians in both major parties—that have significantly reduced drug-approval time and increased the degree of risk-taking on the FDA's part. The most notable change was PDUFA, first enacted in 1992 and subsequently reauthorized three times, most recently in 2007. Several studies, including one recent study by two of Petitioner's Economists, show that this law has accelerated FDA drug approval. See generally Carpenter et al., Web Exclusive; Berndt et al., Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates, 4 Nature Reviews Drug Discovery 545 (2005). Other studies show that the deadlines imposed by these changes are associated with highly abrupt approvals of new medicines and higher rates of postmarket safety problems for drugs once they reach the market. See generally Carpenter et al., Drug Review Deadlines and Subsequent Safety

Problems, 358 New Eng. J. Med. 13:1354 (2008). Additionally, there is evidence linking faster approval times with a higher incidence of adverse drug reactions. Olson, The Risk We Bear: The Effects of Review Speed and Industry User Fees on New Drug Safety, 27 J. of Health Econ. 175, 177 (2008); Olson, Pharmaceutical Policy Change and the Safety of New Drugs, 45 J.L. & Econ. 615, 632-641 (2002). That body of evidence suggests that Petitioner's Economists' characterization of the FDA as excessively cautious, acting too strongly in favor of minimizing Type I error in drug approval, is erroneous.

Petitioner's Economists' argument assumes both that reputational pressure is the overriding (or only) incentive acting on the FDA and that such pressure acts in only one direction. But, as the empirical data confirm, numerous incentives for rapid drug approval and risk-taking also face the agency, at least balancing any incentives for excess caution.

3. Petitioner's Economists Fail to Prove That the FDA's Labeling Policy Does Not Strike the Proper Balance Between Type I and Type II Errors.

Having failed to offer *any* convincing empirical proof that the FDA is overly cautious in its labeling policy, Petitioner's Economists rely entirely on economic theory to make their case. But their theory fails on at least two levels. First, Petitioner's Economists' premise that the FDA errs toward too many Type II errors in drug *approval* is flawed. Secondly, in any event, the sleight of hand by which they attribute the same alleged FDA risk aversion to its drug-*labeling* policy cannot withstand scrutiny.

Even if there were reason to believe that the drug-approval process produces suboptimal outcomes due to risk aversion, there is no basis for concluding that this effect permeates every decision made by the FDA. Indeed, there are no *a priori* reasons to believe that the FDA is excessively risk averse when it comes to regulating product labels because labels that are lacking pertinent information (Type I error) and labels that are so long as to obfuscate interpretation (Type II error) will both receive public scrutiny. The media, consumers, and consumer advocates have proven sensitive to allegedly overly stringent regulations.[10] The Wall Street Journal articles cited by Petitioner's Economists are perfect examples of bad press for the FDA when it requires too much verbiage. Hensley, Long Labels Help Drug Firms, But Can Obscure What Matters, Wall St. J., June 28, 2005; Hensley, Liability Worries Cloud Drug Labels, Wall St. J., July 5, 2005. Thus, Petitioner's Economists are wrong to argue that the FDA errs in the direction of Type II errors only.

Finally, Petitioner's Economists fail to consider the possibility that FDA staff and its advisory

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[10] The public is definitely aware of such Type II errors. For example, a 2006 New York Times article about antidepressants noted criticism by psychiatrists of the FDA's increased warning label requirements. An assistant professor of child psychiatry at Columbia University voiced strong concerns over whether more stringent labeling rules for antidepressants had caused a reduction in antidepressant prescriptions, which in turn could cause an increase in the suicide rate. Carey, Panel to Debate Antidepressant Warnings, N.Y. Times, Dec. 13, 2006, at A30. A 2004 New York Times article noted similar concerns by psychiatrists after the FDA imposed stricter antidepressant labeling rules. Harris, F.D.A. Toughens Warning On Antidepressant Drugs, N.Y. Times, Oct. 16, 2004, at A9.

committees are subject to regulatory capture by drug companies, which would cause staff to tolerate too many *Type I* labeling errors, that is, a bias in the opposite direction. A 2006 study in the Journal of the American Medical Association investigated the financial conflicts of interest at the FDA. See generally Lurie et al., Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings, 295 J. Am. Med. Ass'n 1921 (2006). The study found that, at 73% of drug-related advisory committee meetings over a three-year period, at least one voting scientist present had disclosed a conflict yet only 1% of the advisory committee members were recused. *Id.*, at 1921. About a quarter of the conflicts involving consulting arrangements, contracts or grants, and investments exceeded $10,000, $100,000, and $25,000 respectively. *Ibid.* A "statistically significant positive relationship was apparent for competitor conflict" and voting patterns. *Ibid.;* see also Harris et al., 10 Voters on Panel Backing Pain Pills Had Industry Ties, N.Y. Times, Feb. 25, 2005, at A1. Depending on the severity of this classic regulatory-capture problem, the FDA may be imposing a labeling standard that is *too lenient* relative to the socially optimal standard—that is, $P_{FDA} > P^*$. If that were the case, then any alleged bias introduced by state tort liability would nudge the outcome of Type I and Type II errors toward the socially optimal level.

4. Petitioner's Economists Conflate the Costs of a Type II Error Associated with the FDA's Labeling Policy with Costs of a Type II Error Associated with the FDA's Drug-Approval Policy.

Petitioner's Economists argue that state-tort-law requirements "exacerbate FDA Type II errors" by causing drug manufacturers to "hold back on seeking approval of new drugs or to add defensive labeling." Economists' Br. 13. But they exaggerate the costs of a Type II error related to the FDA's *labeling* policy by drawing on the costs of such an error related to the FDA's *drug-approval* policy. Stated differently, Petitioner's Economists, when attempting to emphasize the possible social costs of Type II errors relating to labeling policy, cannot avoid invoking dynamic effects ("holding back on seeking approval") associated with the FDA's drug-approval policy.

Of the five social costs Petitioner's Economists describe as associated with an "added layer of tort liability overdeterrence," *id.*, at 14, the first two—limited drug availability and disincentives for research and development—*have no connection with the FDA's labeling policy*, and should therefore be ignored here.[11] When considering the Type II error costs associated with the FDA's labeling policy, the only relevant cost to consider in their five-part

[11] Arguably, it is possible that lost sales due to overwarnings could adversely affect a drug manufacturer's profits. But Petitioner's Economists do not make that argument, and no evidence exists that such overwarnings generate sufficiently material losses to induce exit by drug manufacturers.

list is item 4, "Defensive Labeling." *Id.*, at 17.[12] Petitioner's Economists correctly point out that the primary costs associated with defensive labeling relate to overwarning, *i.e.*, discouraging beneficial use of drugs. Petitioner's Economists do not quantify those error costs, and, although it is possible that such costs are economically significant—perhaps when a drug not taken due to overwarning could save a life—there is no conclusive evidence or consensus that they are. Notably, Petitioner's Economists do not even discuss costs related to clutter, presumably because those Type II error costs are not significant.

When the costs of the *relevant* FDA Type II error are considered—and only those costs—the socially optimal standard may be a very stringent labeling standard. It is generally thought that the more information provided to consumers or prescription drugs and their agents (physicians), the more likely it is that decisions made in the marketplace will reflect true economic efficiency—that is, transactions will reflect two parties mutually agreeing to make themselves better off through trade. In the framework developed above, the FDA may optimally choose a P^* that tolerates many Type II errors precisely because the associated Type II error costs are small relative to the costs of Type I errors. Stated differently, what Petitioner's Economists

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[12] The other two alleged Type II error costs—"loss of FDA control over drug labeling" and "problems exacerbated further in state tort cases alleging missing contraindications," Economists' Br. 17, 19—can also be ignored here. Regarding the alleged loss of FDA control, it is not true that state tort liability deprives the medical community of the benefits of FDA expert determinations. And excessive contraindications should be subsumed by the "defensive labeling" category of social costs.

perceive to be an inefficient labeling policy may in fact be the socially optimal policy.

Additionally, failure-to-warn litigation acts in several ways to lessen FDA Type II error in drug approval. Because failure-to-warn litigation incentivizes information disclosure after launch, it is less necessary to have complete information before approval and approval can be more rapid. The safety net offered by failure-to-warn litigation's ability to correct FDA mistakes also enables the FDA to approve promising new products earlier. Further, without the warnings and contraindications incentivized by failure-to-warn litigation, the FDA may decide to withhold approval entirely for some drugs that would otherwise receive warnings on their labels.

5. The FDA Has Taken Active Measures to Counteract Defensive Labeling Relating to State-Level Lawsuits.

Petitioner's Economists implicitly assume that the FDA is insensitive to the potential incentive effects created by state tort liability. In essence, they model the FDA decision-making process as a two-period game in which the FDA determines a labeling standard in period 1 *independent of what takes place in period 2*, and then manufacturers face the prospect of state tort liability in period 2. But any student of game theory recognizes that such behavior is not a stable equilibrium. A more realistic modeling assumption is that the FDA and manufacturers, sophisticated agents, look forward to future possible tort litigation when choosing strategies during the labeling period. See Struve, The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation, 5 Yale J. Health Pol'y L.

& Ethics 587, 587-88 (2005). Such anticipatory strategies contradict the simplistic modeling assumption used by Petitioner's Economists to describe the FDA's calculus. More importantly, the evidence demonstrates conclusively that the FDA is keenly sensitive to allowing too many Type II errors, especially those potentially caused by state tort liability in the "second period" of a multi-period game.

C. Studies Refute Juries' Alleged Bias in State Tort-Liability Trials.

Finally, empirical evidence refutes Petitioner's Economists assertion that juries in state tort lawsuits inject another systematic bias, skewing the process toward accepting even more Type II errors in the labeling process. The blanket claim that juries behave irrationally when deciding tort lawsuits is made without reference to any rigorous systematic evidence.

A recent review by Dr. Neil Vidmar, professor of psychology and law at Duke University, of empirical analyses of jury decisions in matters requiring expert testimony suggests that juries perform effectively even in cases involving complex circumstances:

> Judge and jury agreement was not significantly different than that found by Kalven and Zeisel almost 50 years before. There was little support for a conclusion that legal complexity or evidentiary complexity accounted for disagreement between judge and jury. More general surveys asking national samples of state and federal judges to evaluate jury performance indicated that the overwhelming majority of judges expressed high agreement with verdicts.

Vidmar, Expert Evidence, the Adversary System, and the Jury, 95 Am. J. Pub. Health S137, S139 (2005). In reviewing another study, Dr. Vidmar avers:

> Taragin et al. obtained access to confidential liability insurer files for lawsuits that occurred in New Jersey between 1977 and 1992. In each case, whenever a medical incident that might constitute malpractice was reported to the insurance company, one or more physicians made an assessment of whether negligence occurred. Among cases that eventually went to trial, physician ratings of whether negligence had occurred were positively related to jury verdicts at a statistically significant level.

Id.

Recent studies also demonstrate that medical malpractice litigation tends to allot compensation when an identifiable medical error was committed and tends not to allot compensation when no medical error was committed. When trained physicians reviewed a random sample of 1,452 medical malpractice cases and produced their own judgments as to medical error, the independent analysts' error findings were overwhelmingly correlated with both the fact of compensation and the amount of compensation.[13] In short, the proposition that juries make irrational decisions when confronted with complex evidence is empirically unwarranted.

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[13] Studdert et al., Claims, Errors, and Compensation Payments in Medical Malpractice Litigation, 354 New Eng. J. Med. 19:2024, 2032 (2006) ("Our findings suggest that moves to curb frivolous litigation, if successful, will have a relatively limited effect on the caseload and costs of litigation. The vast majority of resources go toward resolving and paying claims that involve errors.").

Finally, Petitioner's Economists proposition that the purpose of the state tort suits "is to perform a better balancing act than the FDA," Economists' Br. 19-20, is misguided. State tort lawsuits do not compete with the FDA as the economic goal of both is the maximization of social welfare; rather, these lawsuits serve a complementary function.

CONCLUSION

For these reasons and those more fully developed in respondent's briefing, the Court should affirm the judgment of the Vermont Supreme Court. Congress's refusal to preempt state failure-to-warn litigation is demonstrably wise policy. By reducing information imbalances, incentivizing responsible behavior by drug manufacturers, and ameliorating the effects of Type I and Type II errors in drug approval and labeling, state failure-to-warn litigation complements the FDA regulatory regime and increases social welfare.

Respectfully submitted,

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